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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/963,368	11/03/1997	GERRY P. NOLAN	A-64260-2/DJ	9991

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EXAMINER
BHATTI, TAHIRA H

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 04/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/963,368	NOLAN, GERRY P.	
	Examiner	Art Unit	
	Tahira H Bhatti	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10/1/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *16-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/01 has been entered.

2. Claims 16-31 are currently pending

3. Claim 29 was added by amendment /D, filed on 1/2/01.4..

4. New claims 30-31 were added by amendment/E filed on 10/1/01.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. (This is a new matter rejection).

The new claim (claim 29) represents a departure from the specification as originally filled. It is drawn to a library of cells expressing randomized polypeptides intracellularly. There is no direction given, between delivery of specific peptides to subcellular or intracellular organelle and the random intracellular expression of a library of peptides.

Hence adequate support for the invention of claim 29 was not found in the instant specification and the claim constitutes new matter.

7. Claim 16-28 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for molecular library of retrovirus comprising of randomized nucleic acid encoding a plurality of randomized peptides and a cellular library containing a molecular library of retroviral constructs, comprising of randomized nucleic acids, does not reasonably provide enablement for the molecular library of retroviral constructs, encoding a plurality of randomized peptides and the cellular library of retroviral constructs, integrated into cellular genome consisting of fusion partner. The said fusion partner comprising of targeting sequence, rescue sequence, stability sequence and a dimerization sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in a determination of undue experimentation are disclosed in In re Wands (USPQ 2d 1400: CAFC 1988), which include:

a. The breadth of the claims. b. The nature of the invention. c. The state of the prior art. d. The level of one of ordinary skill. e. The level of predictability in the art. f. The amount of direction provided by the inventor. g. The presence or absence of working examples h. The quantity of experimentation necessary needed to make or use the invention based on the disclosure. See :In re Wands USPQ 2d 1400 (CAFC 1988).

The breadth of the claims: The breadth of potential for obtaining a molecular library of retroviruses, comprising of randomized nucleic acids encoding a plurality of

randomized peptides and a cellular library of mammalian cells containing a molecular library of retroviral constructs, encoding a plurality of randomized peptides. Wherein said nucleic acids further encode a fusion partner, as encompassed by claims 16-23 (especially claim 1) is huge in light of the failure to specifically claim the metes and bounds regarding the production of candidate bioactive agent, expressed in the cellular library.

The nature of the Invention/State of the Prior Art: The present invention as claimed is broadly directed to a method and compositions for screening for a candidate bioactive agent and accesses molecules or targets within living cells and provide for the selection of those bioactive agents with desired phenotypic effects. In this regard it is further noted, that critical or essential parameters to practice the invention, but not included in the claim(s), is not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); Ex parte Bide (BdPatApp&Int) 42 USPQ2d 14.

The amount of direction/working examples: The specification only provides guidance and examples directed to the method of obtaining a cellular library containing a molecular library of retrovirus constructs, wherein said construct are integrated into the cellular genome encoding a plurality of randomized peptides. This does not provide enough guidance as to the specific genomes or a specific sequence of molecules, which would selectively be inserted to encode a specific peptide. This is not representative of the scope of claimed methods, for screening and selecting a candidate bioactive agent envisioned to have pharmacological applications.

Quantity of Experimentation: Due to the lack of representative examples regarding the method of obtaining randomized nucleic acids encoding plurality of randomized peptides and fusion partner (targeting sequence, rescue sequence, stability sequency and a dimerization sequence) of a representative sample of a set of molecules the amount of experimentation would be undue.

Accordingly, in light of the unpredictability surrounding the method of obtaining the molecular library of retroviruses and a cellular library of retrovirus constructs encoding a plurality of peptides in mammalian cells and screening the plurality of cells for a cell exhibiting an altered phenotype, wherein the altered phenotype is due to the presence of a bioactive agent, the undue breadth of the claimed invention, the lack of adequate guidance, the lack of metes and bounds regarding claimed constituents, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation.

8. *The following is a quotation of the second paragraph of 35 U.S.C. 112:*

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim16-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "Randomized peptides" and "randomized nucleic acids" (claims 16-21), are vague, Randomization covers enormous field, and in the specification there is lack of directional guidance for specificity. Similarly in claim 22, ("constructs" and "cellular genome") sufficient information on specific structure, sequence of cellular genome or other identifying characteristics is lacking.

Claims 23-27 are rejected because of the fusion partner being consisted of "a targeting sequence", "a rescue sequence", "a stability sequence" and "a dimerization sequence". These fusion partners are each different from one another and consist of many variations in each group, which are not disclosed sufficiently in the specification. It does not disclose which amino acids are intended; it deals with a class that is enormous.

10. The following is a quotation of 35 U.S.C. 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 16-22 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jellis et al, Gene 137: 63-68 (1993), in view of Kauffman U.S.patent No: 5,723,323 and Drunker et al, Nucleic Acid Res. 19: 6855-6861, (1991).

Jellis et al reference teaches a phage display library expressing 1.5×10^8 unique random 20 amino acid peptides fused to a coat protein, which is isolated and identified by DNA sequences. He teaches that isolating and identifying the diverse random peptides would successfully identify the peptide that binds to target molecule of interest (page 63-65). Jellis et al, do not teach a retrovirus library.

Kauffman et al teach construction of a molecular library that is the same as that disclosed by Jellis except that DNA fragment is introduced into the cell using retrovirus, which results in transducing genes nearly into 100% of host cells (claim 21) and into a variety of species. Kauffman further discloses that DNA intermediate of retroviruses can

integrate into host chromosomes (claims 22) by inserting a gene of interest into host genome (page 494 particular).

Drunker et al teach the use of a retroviral expression library comprising randomized point mutations (page 6860, first paragraph of "Discussion" in particular) in a cDNA coding for polyoma middle T antigen (MTAg). He teaches that the retrovirus insert would lead to the morphological changes associated with the expression of a protein page 6858 col. 2 lines, 12-18 (claim 30). The Drunker et al library is biased for "studying the transforming ability of MTAg" (Abstract in particular).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the random peptide library as disclosed by Jellis and use retroviral-mediated gene transfer method as disclosed by Kauffman and combine it with the techniques of gene isolation, modification and transfer into retrovirus as disclosed by Drunker. Because of the well known technique of gene transfer through retrovirus which is a high efficient method, used for transfer of genetic material into appropriate host cells, one of ordinary skill in the art would be motivated to introduce the molecular library of randomized candidate nucleic acid into plurality of cells, and screen the cells which exhibit altered phenotype and are enable for the production of candidate bioactive agent, envisioned to have pharmacological and biological applications.

12. Claims 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jellis, Kauffman and Drunker as applied to claims 16-22, 28 and 30-31 and further in view of reference, Nilsson et al, Curr. Opin. Struc. Biol. 2:568-575 (1992).

Jellis, Kauffman and Drunker have been discussed supra. However, these references do not teach 'fusion' proteins.

Nilsson et al teach that, for the construction of a large and diverse library, it is important to use the fusion protein technique. He discloses that fusion proteins (claims 23-26) are constructed for a variety of purposes, such as increasing the stability of the product (claim 26), both during purification or in vivo use of the product (page 570-571 in particular). Nilsson et al teach that a protein of interest is fused between two different "affinity handle proteins", that has unique binding characteristics, which facilitates purification (rescue,) of the desired protein so that the protein which confers a particular phenotype of interest on the host cell can be isolated for further study (claim 25). Additionally, Nilsson et al further disclose that the reason to construct a fusion protein is, that, fusion proteins when fused to a drug molecule to target a drug to a specific cell type is an important application of the fusion protein technology (page 572 in particular) [claim 24].

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made and having the benefit of the teachings of Nilsson et al, to introduce the molecular library of retroviruses of randomized candidate nucleic acids into plurality of cells, and screen the said cells for altered phenotypes. One would have been motivated with a reasonable expectation of success to take it further to use fusion protein techniques (which covers a wide rang of applications, e.g. purification, enhanced solubility, stability, targeting etc) for the construction of the molecular library based on the teachings of Nilsson et al. One would have been motivated to combine these

teachings with a reasonable expectation of success to construct the retrovirus library with fusion protein to access molecules or targets within living cells for variety of reasons ranging from protein recovery to therapeutic uses. Claim 27 is included because dimerization of a recombinant peptide is well known in the art to be effective for increasing the immunogenicity of antigenically weak peptides, which are of interest as potential immunospecific targets to treat a particular condition.

13. Applicant's arguments with respect to claim 16-31 have been considered but are moot in view of the new ground(s) of rejection.

14. No claims are allowed.

General information regarding further correspondence

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Tahira Bhatti whose telephone number is (703) 605-1203.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsana Venkat (art unit 1627), can be reached at (703) 308 0570 .

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (702) 308-0196 .

Tahira Bhatti (art unit 1627)
Jan. 22nd. 2002

PADMASHRI PONNALURI
PRIMARY EXAMINER
for SPE